Journal of Neuroradiology 49 (2022) 219–224

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Imaging markers of intracranial aneurysm development: A systematic review

Angelina K. Kancheva[a,*], Birgitta K. Velthuis[b], Ynte M. Ruigrok[a]

[a] Brain Center Rudolf Magnus, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht University, the Netherlands
[b] Department of Radiology, University Medical Center Utrecht, Utrecht University, the Netherlands

ARTICLE INFO

Article History:
Available online 8 October 2021

Keywords:
Imaging marker
Intracranial aneurysm
Neuroimaging
Subarachnoid hemorrhage

ABSTRACT

Background: Imaging markers of intracranial aneurysm (IA) development are not well established.
Purpose: To provide an overview of imaging markers of IA development.
Methods: A systematic search of PubMed and Embase up to December 1st 2020 using predefined criteria. Thirty-six studies met our inclusion criteria. We performed a quantitative summary of the included studies.
Results: We found converging evidence for A1 segment asymmetry as an anatomical marker of anterior communicating artery (Acom) aneurysm development, and moderate evidence for several other markers. No hemodynamic markers yielded converging or moderate evidence. There was large heterogeneity across studies, especially in the definitions of imaging markers and study outcomes used. Due to the poor methodological quality of many studies and unavailability of effect sizes or crude data to calculate effect sizes, a formal meta-analysis was not possible.
Conclusions: We only identified A1 segment asymmetry as an imaging marker of Acom aneurysm development with converging evidence. A meta-analysis was not possible due to the heterogeneity of marker definitions and outcomes used, and poor methodological quality of many studies. Future studies should use robust study designs and uniformly defined imaging markers and outcome measures.

Introduction

Approximately 3% of the population harbors an unruptured intracranial aneurysm (IA) .[1] Rupture of an IA causes subarachnoid hemorrhage (SAH). This subtype of stroke has an incidence of around eight cases per 100 000 person-years.[2] Although SAH accounts for only about 5% of all incident strokes, it carries a substantial disease-specific burden.[3]

The pathogenesis of intracranial aneurysms (IAs) remains insufficiently understood.[4] Several imaging markers related to aneurysm growth – and thereby a higher risk for rupture – have been well-established, such as initial aneurysm size, aneurysm location, and irregular aneurysm shape.[5] However, fewer studies have investigated imaging markers that constitute risk factors for aneurysm development. Given that most IAs never rupture,[6] it is important to determine risk factors for aneurysm development separately from risk factors for rupture. Insight into imaging markers for IA development may help guide frequency of screening and preventive management in individuals at a higher risk for aneurysm formation, such as first-degree relatives of SAH patients.[6] The aim of the current investigation was to systematically review studies on two categories of imaging markers of IA development, namely anatomical and hemodynamic markers.

Methods

Search strategy and selection criteria

Studies were identified by systematically searching PubMed and Embase until December 1st 2020 using different combinations of the relevant keywords (see Supplementary Material, Supplementary Figure 1 for the full electronic search strategy) following the

Abbreviations: ACA, anterior cerebral artery, Acom, anterior communicating artery; BA, basilar artery; IA, intracranial aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; Pcom, posterior communicating artery; VA, vertebral artery; WSS, wall shear stress

Disclosure of Funding We acknowledge the support from the Netherlands Cardiovascular Research Initiative: An initiative with support of the Dutch Heart Foundation, CVON2015-08 ERASE. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No. 852173).

Conflict of Interest None.

* Corresponding author at: Brain Center Rudolf Magnus, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Heidelberglaan 100.
E-mail address: angelina.k.kancheva@gmail.com (A.K. Kancheva).

https://doi.org/10.1016/j.neurad.2021.09.001

Table 1
Methodological quality score.

Methods		Points
Design	Prospective cohort study (3 points) Retrospective cohort study or case-control study with consecutive cases from prospective database (2 points) Case-control study with consecutive cases from retrospective database (1 point) Non-consecutive case-control study (0 points)	3
Population	Baseline characteristics described for all patients, participants recruited from multiple centers (2 points) Baseline characteristics described for all patients, participants recruited from single center (1 point) Baseline characteristics not fully/clearly described, participants recruited from single center (0 points)	2
Study aim	Primary aim was to investigate relationship between a well-defined anatomical or hemodynamic marker and intracranial aneurysm development	1
Sample size	>100 study participants, balanced number of cases and controls (close to 1:1 ratio) (2 points) Limited sample size (n<100) but balanced number of cases and controls (close to 1:1 ratio) or sample size >100 but unbalanced number of cases and controls (1 point) Limited sample size (n<100) and unbalanced number of cases and controls (0 points)	2
Data analysis and presentation		
	Statistical analyses included multivariate analysis with control for potential confounders; OR with 95% CIs reported (2 points) Only descriptive statistics reported per outcome (e.g., means and SDs, medians and IQRs) (1 point) Narrative reporting of results (0 points)	2
Score	<7 points=low quality; 7–10 points=high quality	**10**

CI=confidence interval; IQR=interquartile range; OR=odds ratio; SD=standard deviation.

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations. Studies were included if they reported on the association between an imaging marker for IA development and if they used a control group that did not harbor IAs. Studies were excluded if they were (1) case reports describing less than ten patients, review papers, conference abstracts, or letters to the editor, (2) mathematical models, (3) animal studies, or (4) in languages other than English. To assess the eligibility of the identified articles, A.K.K. screened the titles, selected relevant abstracts, and if necessary, the full text, on inclusion and exclusion criteria. Eligibility assessment was cross-checked by Y.M.R. Disagreements between investigators were resolved by consensus. Reference lists of relevant articles were searched for additional publications until no further publications were found.

Data extraction

Studies were grouped into two categories of imaging markers, namely anatomical and hemodynamic markers. The following information was extracted from each study: (1) author and year of

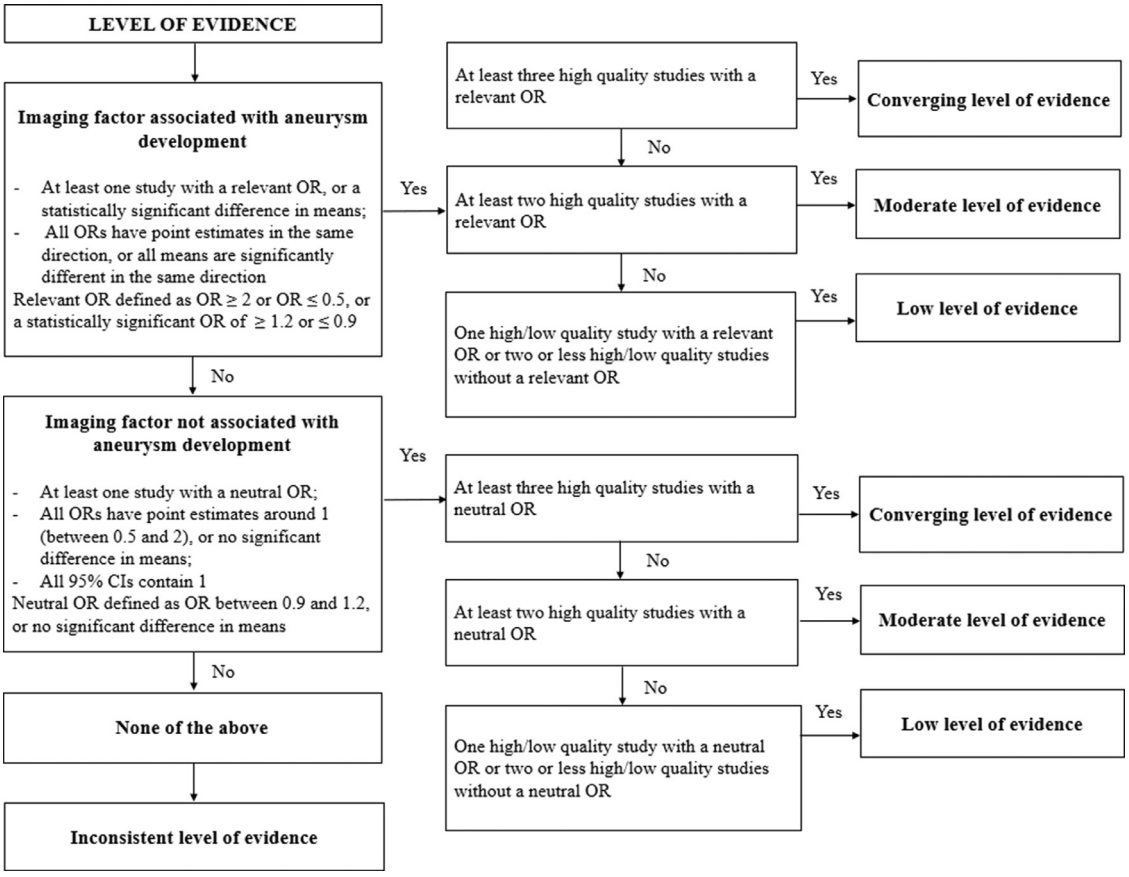

Fig. 1. Categories for level of evidence of imaging factors.
OR stands for odds ratio.

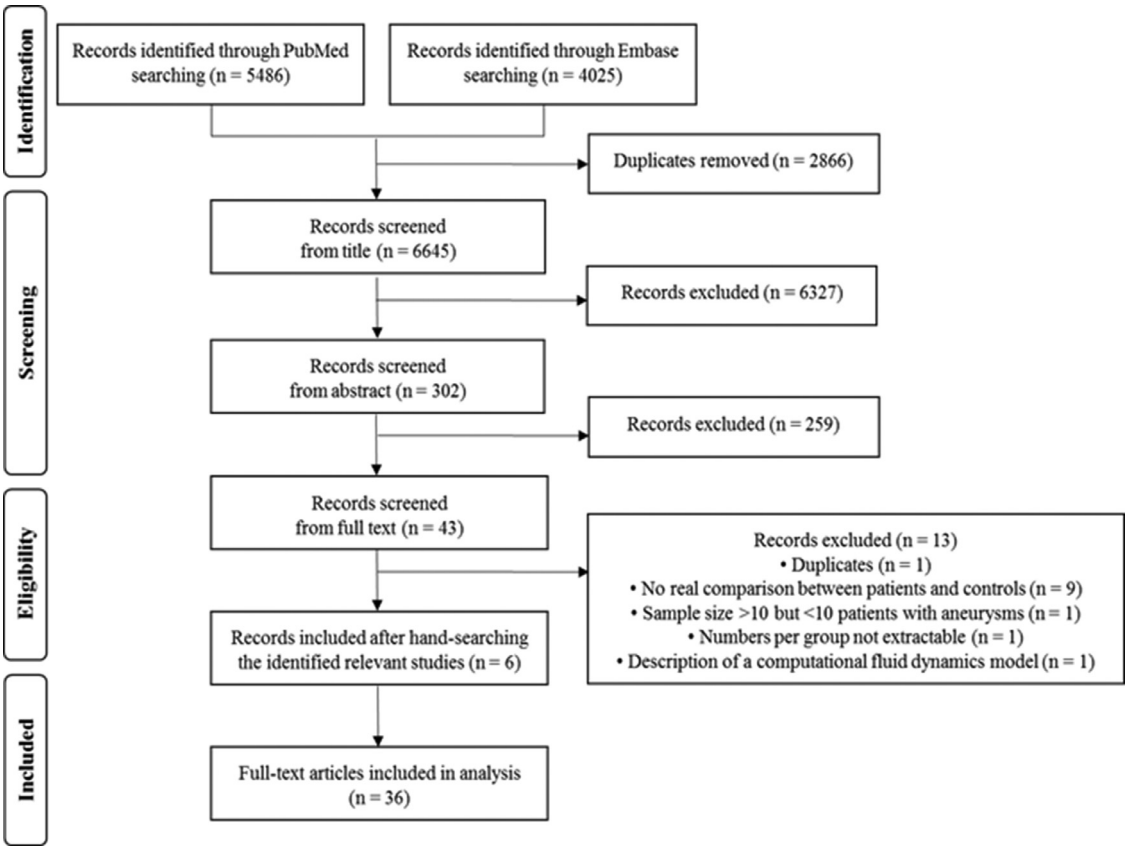

Fig. 2. Flow diagram detailing the selection of studies.

publication, (2) study design (i.e., cohort or case-control, prospective or retrospective, single-center or multicenter, consecutive cases or not, etc.), (3) population, (4) study aim, (5) outcome measure(s), (6) sample size, (7) exact number of patients and controls (if extractable), (8) data analysis (i.e., statistical method used), and (9) data presentation of the results (i.e., effect size measure(s), e.g., odds ratios, risk ratios, etc., and/or means with corresponding standard deviations or confidence intervals). Data extraction was performed by A.K.K. and cross-checked by Y.M.R. Disagreements between the two authors were resolved by discussion.

Quality and level of evidence assessment

Quality assessment of the studies was performed using an adapted version of a previously published methodological quality score,[7] which was modified for the purposes of the current review (Table 1). Studies with scores between 7 and 10 points were considered to be high quality studies, and studies with scores below 7 points to be low quality. Additionally, level of evidence for the association between each imaging marker and IA development was assessed using an adapted version of previously published categories for level of evidence of risk factors associated with IA rupture.[5] Imaging markers were categorized as either associated or not associated with IA development. Level of evidence was categorized into converging, moderate, low, or inconsistent (Fig. 1). The methodological quality and level of evidence was assessed by A.K.K. and cross-checked by Y.M.R.

Analysis

We performed a quantitative summary of the identified imaging markers. Our aim was to also perform a formal meta-analysis by calculating pooled odds ratios with corresponding 95% confidence intervals for markers associated with aneurysm development, but the large heterogeneity across studies precluded such an analysis.

Results

Characteristics and methodological quality of studies

After screening 9522 publications, we identified 36 eligible studies (Fig. 2) reporting on 8497 study participants (3529 cases and 4968 controls). These studies included 33 case-control design studies (7 prospective and 26 retrospective), 1 retrospective cross-sectional design, and 1 prospective cohort study. General characteristics of all extracted studies, including study design, population, study aim, outcome measure(s), data analysis, results, main study limitations, and methodological quality score, are provided in Supplementary Material, Supplementary Table 1.

Seventeen studies fulfilled our criteria for high quality and 19 studies for low quality (Supplementary Table 1). Relatively few studies (n = 15) included multivariate analyses (Supplementary Table 1).

There was large heterogeneity across studies, especially in the definitions of imaging markers and study outcomes used. As a result, we were not able to perform a formal meta-analysis for any of the markers. In addition, most studies only examined IAs of one cerebral artery instead of all IAs of all cerebral arteries comprising the circle of Willis. A detailed narrative synthesis of the main findings of each study is provided in a tabular format in Supplementary Table 2. In the following paragraphs, we only report the markers with converging and moderate level of evidence. Markers with low level of evidence are presented in Table 2. Markers that were found not to be associated with aneurysm development are presented in Table 3.

Table 2
Anatomical and hemodynamic imaging markers associated with aneurysm development with low level of evidence.

Anatomical Imaging Markers
Anterior cerebral artery (ACA)/Anterior communicating artery (ACOM)
✓ Wider Acom/A2 bifurcation angle[36]
✓ Smaller A1-A2 angle on aneurysm side[8,37]
✓ Smaller Acom diameter[36]
Middle cerebral artery (MCA)
✓ Narrowed lateral angles of M1 and superior and inferior M2 branches[38]
✓ MCA with high curvature[17,38]
✓ Angle between post-bifurcation branches[39]
✓ Wider MCA bifurcation inclination angle (i.e., angle between parent vessel plane and daughter branches plane)[18]
✓ Smaller M1-M2 vessel angle[17]
✓ Least and most deviating angle of MCA bifurcations[33]
✓ Smaller M1 diameter[17]
✓ Lower M1 and M2 widths[38]
✓ MCA junction exponent (a measure of adjustment of a given vascular system to its theoretical optimum value of 3 obtained with an online calculator)[39]
✓ M1 segment tapering[40]
Posterior cerebral artery (PCA)/Posterior communicating artery (Pcom)
✓ Fetal type Pcom (Type P) (i.e., PCA continuously delineated from internal carotid artery through Pcom; also called embryonal type)[41]
✓ Smaller angle between C6 (ophthalmic segment extending to origin of Pcom) and C7 (terminal communicating segment) segments of ICA[41]
✓ Type A anatomical variation of the Pcom (i.e., no visualization of unilateral P1 segment)[42]
✓ Larger Pcom diameter[43]
Internal carotid artery (ICA)
✓ ICA abnormal vascular caliber control (i.e., focal dilations of the extra- and intracranial ICA upstream of IA location)[44]
Basilar artery (BA)
✓ Basilar tip tortuosity[45]
✓ Higher sum of angle metrics (i.e., sum of BA angles divided by the length of the curve representing the BA course)[21]
✓ Higher triangular index (the BA curve represents a triangle and the sum of its sides is divided by its base, and is then divided by the number of BA sub-curves)[21]
✓ Greater product of angle distance (sum of angle metrics divided by BA relative length, the straight line between the start and end points of the BA divided by the curve length)[21]
✓ Increased inflection count metrics (number of inflection points of the curve divided by the straight line between the start and end points of the BA)[21]
IAs at remaining cerebral arteries
✓ Increased cervical artery tortuosity[46]
✓ Posterior inferior cerebellar artery aplasia[47]
Hemodynamic Imaging Markers
ACA/ACOM
✓ Wall shear stress of parent artery (stress exerted by blood flow on vessel wall) between 7.8 and 12.3 dyne/cm2[31]
✓ Lower Acom pulsatility index (calculated as the peak systolic velocity and end-diastolic velocity of the vessel)[9]
✓ Greater brachial–ankle pulse wave velocity (measure of speed of a blood pressure wave between two given sites of an artery, which reflects arterial stiffness)[48]
MCA
✓ Volume flow rate, defined as mean flow velocity in MCA[39]
ICA
✓ Increased carotid artery augmentation index (i.e., proportion of central pulse pressure due to late systolic peak, which is attributed to reflected pulse wave; an indirect measure of arterial stiffness)[49]

IA=intracranial aneurysm.

Table 3
Anatomical imaging markers not associated with aneurysm development with low level of evidence.

Anatomical Imaging Markers
Middle cerebral artery (MCA)
✓ MCA vascular variations, i.e., (1) normal MCA with superior and inferior branches, (2) accessory MCA, (3) duplicating MCA, and (4) fenestrations of MCA[50]
✓ MCA bifurcation configuration before the genu[51]
✓ Smaller MCA parent-to-daughter artery angles[52]
✓ Larger MCA daughter-to-daughter angles[52]
✓ Longer MCA segment lengths[52]
✓ Increased MCA tortuosity[20]
Basilar artery (BA)
✓ Asymmetry of the P1 segment and VAs[53]
✓ Absence of fetal type PCA[54]

PCA=posterior cerebral artery; VA=vertebral artery.

Anatomical imaging markers associated with aneurysm development

Converging level of evidence

Converging evidence was found for asymmetry of the A1 segment (proximal portion of the anterior cerebral artery) as a marker for the development of anterior communicating artery (Acom) IAs, which was assessed in seven studies[8–14] (OR range of 2.5–7.6 based on two studies[9,10]). These seven studies reported on a total of 1660 participants, of whom 848 were patients (626 with Acom IAs or IAs within the A1-A2 junction, 59 patients with posterior communicating artery (Pcom) IAs, 40 with middle cerebral artery (MCA) IAs, and 123 with other IAs) and 812 controls (subjects who underwent cerebral angiography for multiple reasons, but no IAs were identified during angiographic evaluation). Two of the seven studies had a prospective case-control design,[8,12] of which one was multi-center,[8] while the other five had a retrospective case-control design.[9–11,13,14] The average duration of follow-up was 5.57 years. A meta-analysis was not possible due to the use of different definitions of A1 asymmetry across the studies (see Table 4 for the different definitions of A1 asymmetry).

None of the identified markers yielded converging evidence for the development of MCA, PCA/Pcom, internal carotid artery (ICA), vertebral artery (VA), or basilar artery (BA) IAs.

Moderate level of evidence

Moderate evidence was found for increased A1-A2 vessel diameter ratio as a risk factor for Acom IA development.[15,16] A meta-analysis was not possible due to the unavailability of ORs or crude data to calculate ORs. Additionally, moderate evidence was found for wider MCA bifurcation angle (angle between M2 segments) as a marker for MCA IA development, but no OR was reported.[17,18] When it comes to markers for ICA IA development, moderate evidence was found for increased curvature of the ICA.[13,19] A meta-analysis was not possible due to the different ICA curvature definitions (measured either as the carotid siphon angle formed by the intersection of two lines traced from intracavernous and supraclinoid points through the artery,[13] or as mean and peak curvature in mm – caudal and distal from the ICA bifurcation[19]) and the unavailability of ORs or crude data to calculate ORs. Lastly, moderate evidence was also found for increased BA tortuosity as a risk factor for BA IA development (i.e., elongated BA marked by twists and bends).[20,21]

Table 4
Summary of definitions of A1 asymmetry used.

Author (year)	Definition of A1 asymmetry
Bourcier (2017)[3] Kaspera (2014)[32]	Vascular asymmetry coefficient between 10% and 40%
Tarulli (2010)[32]	A1 anatomic configuration with one A1 providing all or most of the A2 flow (termed A1 dominance)
Charbel (1991)[11]	One A1 filling both A2s, while the contralateral A1 fills neither A2 or only the A2 on its side
Flores (2013)[12]	Presence of a hypoplastic or absent contralateral A1 with the contralateral A2 filling through the Acom complex
Krasny (2014)[14]	Anterior cerebral artery diameter variations in terms of grades: 0=no variation; *I*=diameter is 3/4; II=diameter is 1/2; III=diameter is 1/3 of opposite side

None of the identified markers yielded moderate evidence for IA development of the PCA/Pcom or VA.

Hemodynamic imaging markers associated with aneurysm development

No articles meeting our inclusion criteria assessed hemodynamic markers for PCA/Pcom, VA, and BA IAs independently. None of the identified markers yielded converging or moderate evidence for the development of anterior cerebral artery (ACA)/Acom, MCA, or ICA IAs.

Discussion

We only found converging evidence for A1 segment asymmetry as an anatomical imaging marker of Acom IA development. However, a meta-analysis was not possible due to the use of different definitions of A1 asymmetry across the identified studies. Other anatomical markers, namely increased A1-A2 vessel diameter ratio, wider MCA bifurcation angle, higher BA tortuosity, and increased curvature of the ICA were associated with IA development with moderate evidence at these respective locations. All remaining anatomical markers yielded low evidence. We only identified hemodynamic markers associated with IA development with low evidence. Due to the large heterogeneity across studies and little consistency in marker definitions, we were not able to perform a formal meta-analysis. Therefore, our results should be interpreted with caution.

The rare anatomical markers azygos ACA (single midline A2 segment) ,[22] triplicate A2 segment of the ACA (extra median artery of the corpus callosum) ,[23] and fenestrations of the intracranial vertebrobasilar system[24,25,26] have also been proposed as risk factors for the development of IAs. However, although these markers warrant further investigation, the identified relevant studies[22-26] did not meet our inclusion criteria.

Based on the quantitative summary and narrative synthesis, it can be hypothesized that IAs develop due to violation of the *optimality principle*.[27] According to this hypothesis, blood flow is laminar in straight arterial segments,[28] resulting in a uniformly distributed wall shear stress (WSS) along the vessel wall.[29] Uniform WSS induces feedback mechanisms, which minimize the effects of external hemodynamic stresses.[30] However, WSS may become disturbed at branching points like the ACA/Acom,[18,31] bifurcations like the MCA,[32] and curved regions in the circle of Willis,[33] where hemodynamic forces are no longer uniform. Blood directed from wider bifurcations and asymmetrical arteries to side branches hits the apex at the bifurcation points, which increases local pressure and causes spatially fluctuating flow.[34] Over time, such impinging flow may lead to IA development.[30]

A strong aspect of this study is that it constitutes a comprehensive, systematic review of imaging markers of IA development. The main limitation is that we based our conclusions on mostly retrospective studies with an overall poor quality, which did not implement multivariate statistical analyses, and varied in assessed outcome measures (see Supplementary Table 1 and Supplementary Table 3). Additionally, less than half of the included studies reported effect sizes, which prevented us from performing a formal meta-analysis.

An important conclusion we can draw from our study is that the relevance of many of the identified markers could not be ascertained due to the heterogeneous definitions of imaging markers and outcome measures used across studies. Consequently, our review highlights the need to establish guidelines regarding how to define such measures in a uniform manner. Efforts in this direction have already been made by the National Institute of Neurological Disorders and Stroke and the National Library of Medicine with the Common Data Elements (CDE) Project for Unruptured Intracranial Aneurysms and Subarachnoid Hemorrhage Clinical Research,[35] which has the potential to alleviate the challenges of heterogeneity by providing standardized protocols that facilitate research translation into clinical practice.

Furthermore, future studies should employ robust study designs and statistical methods to clarify the role of imaging markers, which have already been suggested to facilitate IA development, but have not yet been robustly established (i.e., provide not only information on the reliability of their results, such as correlation coefficients and *p*-values, but also report the sizes of their observed effects). Knowledge on which imaging markers are robust risk factors for IA development may help guide optimal preventive screening of first-degree relatives of SAH patients, for whom screening has been shown cost-effective.[6] For example, when no aneurysm is identified at first screening in screening candidates but imaging reveals an imaging marker that puts individuals at a higher risk of developing an aneurysm, it may be reasonable to intensify the intervals between follow-up screenings. This should be the subject of future research.

Last but not least, to facilitate research translation into clinical practice, it is also imperative that more long-term prospective investigations in larger populations are conducted.

Conclusions

We only found converging evidence for A1 segment asymmetry as an anatomical imaging marker of Acom IA development, and moderate evidence for several other markers. No hemodynamic markers yielded converging or moderate evidence. Many studies had poor methodological quality and varied in the definitions of imaging markers and study outcomes used, and did not report effect sizes or crude data to calculate effect sizes. This prevented us from performing a formal meta-analysis. We conclude that more research is needed to clarify the role of anatomical and hemodynamic factors in IA development. Future studies should address the limitations of current research to help establish robust imaging markers, and facilitate research translation into clinical practice.

CRediT authorship contribution statement

Angelina K. Kancheva: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Birgitta K. Velthuis:** Writing – review & editing. **Ynte M. Ruigrok:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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